Courtesy Copy of Biogen Idec Inc.'s opposition of EP Patent No. 1141274

Notice of Opposition to a European Patent

To the European Patent Office

Tabulation marks

for EPO use only

I. Patent opposed

Opp. No. OPPO (1)

Patent No. 1 141 274

Application No. 00902354.0

Date of mention of the grant in the European Patent Bulletin (Art. 97(4), 99(1) EPC) 10 September 2003

Title of the invention:
Soluble Receptor BR43x2 and Methods of Using them for Therapy

II. Proprietor of the Patent ZymoGenetics, Inc.

first named in the patent specification

Opponent's or representative's reference (max. 15 spaces) 0003547EP OREF

III. Opponent OPPO (2)

Name / Address:
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US

State of residence or of principal place of business: US

Telephone/Telex/Fax:

Multiple opponents: ☐ further opponents see additional sheet

IV. Authorisation

1. Representative (Name only one representative to whom notification is to be made) OPPO (9)

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Additional representative(s): ☒ (on additional sheet/see authorisation) OPPO (5)

2. Employee(s) of the opponent authorised for these opposition proceedings under Art. 133(3) EPC — Name(s):

Authorisation(s):
☒ not considered necessary
☐ has/have been registered under No.
☐ is/are enclosed

To 1./2.

EPO Form 2100.1 04.93 (rt. 80, 12/97)

V. Opposition is filed against — for EPO use only

— the patent as a whole [X]

— claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

— it is not new (Art. 52(1); 54 EPC) [X]

— it does not involve an inventive step (Art. 52(1); 56 EPC) [X]

— patentability is excluded on other grounds, i. e. Art. [ ]

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). [X]

(c) the subject-matter of the patent opposed extends beyond the content of the application/ of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). [ ]

VII. Facts and arguments
(Rule 55(c) EPC)
presented in support of the opposition are submitted herewith on a separate sheet (annex 1) [X]

VIII. Other requests:

IX. Evidence presented

Enclosed = ☐

will be filed at a later date = ☒

for EPO use only

A. **Publications:**

Publication date

1

Particular relevance (page, column, line, fig.):

2

Particular relevance (page, column, line, fig.):

3

Particular relevance (page, column, line, fig.):

4

Particular relevance (page, column, line, fig.):

5

Particular relevance (page, column, line, fig.):

6

Particular relevance (page, column, line, fig.):

7

Particular relevance (page, column, line, fig.):

Continued on additional sheet ☐

B. **Other evidence**

Continued on additional sheet ☐

X. Payment of the opposition fee is made — for EPO use only

- [ ] as indicated in the enclosed voucher for payment of fees and costs (EPO Form 1010)
- [x] Please debit deposit account 2805.0059 (Carpmaels & Ransford)

XI. List of documents

Enclosure No.		No. of copies	
0	[x] Form for notice of opposition	2	(min. 2)
1	[x] Facts and arguments (see VII.)	2	(min. 2)
2	Copies of documents presented as evidence (see IX.)		
2a	[ ] — Publications		(min. 2 of each)
2b	[ ] — Other documents		(min. 2 of each)
3	[ ] Signed authorisation(s) (see IV.)		
4	[ ] Voucher for payment of fees and costs (see X.)		
5	[ ] Cheque		
6	[x] Additional sheet(s)	2	(min. 2 of each)
7	[ ] Other (please specify here):		

XII. Signature of opponent or representative

Place LONDON

Date 10 June 2004

MERCER, Christopher Paul

Please type name under signature. In the case of legal persons, the position which the person signing holds within the company should also be typed.

ADDITIONAL SHEET

The following additional representatives are nominated:

CARPMAELS & RANSFORD PROFESSIONAL ASSOCIATION No. 182, and

HOWICK, Nicholas Keith;
FISHER, Adrian John;
MERCER, Christopher Paul;
HALLYBONE, Huw George;
JACKSON, Richard Eric;
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JAMES, Anthony, Christopher W. P.;
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1. Introduction

1.1. I refer to the attached Notice of Opposition (Form 2300) which indicates that an Opposition against EP-B-1 141 274 (the Patent) has been filed by Biogen Idec Inc. (the Opponent).

1.2. The Patent is opposed to the extent of all 38 of its Claims and in respect of all designated states.

1.3. The Opposition Fee is to be debited from our Deposit Account, in accordance with the instructions given on the accompanying Form 2300.

1.4. The remainder of this document sets out the reasons the Opponent believes that the Patent should be revoked under Article 100(a) (lack of novelty and lack of inventive step) and Article 100(c) (Insufficiency).

1.5. In the present letter, the Opponent will refer to the documents listed in the Notice of Opposition, using the numbers referred to therein.

2. Requests

2.1. It is requested that the Patent be revoked in its entirety.

2.2. If the Opposition Division should feel minded to maintain the Patent in any form, Oral Proceedings are requested.

3. The Claims

3.1. Claims 1-28 of the Patent are in "second medical use" format. According to Decisions T4/98 and T854/97, it is necessary to look very carefully at "second

medical use" claims to determine which features are relevant to the scope of the claim and which are not. According to Decision T584/97, the only relevant parts of a claim are the identification of the active substance, the identification of a therapy and the use of the approved claim format. In that case, the claim under consideration had a large amount of wording concerning the form of the medicament. However, the Board of Appeal in that case held that, despite all its additional wording, the claim covered the use of nicotine (the active substance) in the preparation of a medicament for treating conditions susceptible to nicotine therapy (the medical use).

3.2. In T4/98, the claim in question did not recite a therapeutic use at all. It referred to the amount of an unspecified therapeutic compound present in the medicament. The Board held such a claim to be unallowable because it did not identify a compound or a therapy.

3.3. In both cases, the Board referred to the fact that a second medical use claim must refer to a method of the type defined in Article 52(4) EPC.

3.4. Looking at claim 1 in the Patent, it is no doubt the case that it is in proper format.

3.5. It is <u>not</u> clear, however, that it specifies a therapy. The compound is to be used:

"…. for inhibiting ztnf4 activity in a mammal".

This is not, as such, a therapy. The same is true of claim 3 which does not specify a therapy. Thus, in accordance with T4/98, claims 1 and 3 are clearly not in "second medical use" format.

3.6. Therefore, as claims 1 and 3 do not define a therapy, they must be construed to cover a method in which the specified compounds are used in the production of a medicament. The reference to "ztnf4 activity" or "inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement" must be ignored.

4. Priority

None of the claims that refer to TACI are entitled to their claimed priority date as TACI as referred to in the priority document US 09/226,533 is different to that referred to in the application as filed (WO 00/40716). This can clearly be seen by comparing the recited sequence for TACI in the priority document (SEQ ID NO: 5) which is 199 amino acids long, with that recited in the application as filed (SEQ ID NO: 6) which is 293 amino acids long!

4.1. Claim 1 is not entitled to the claimed priority of 7th January 1999.

4.1.1. The priority document does not mention a soluble polypeptide comprising the extracellular domain of TACI (part b). The priority document does refer to a fragment of TACI that consists of amino acids 1-166. However, it is not clear from the disclosure whether this is the extracellular domain of TACI, and there is nothing which indicates whether or not this fragment is soluble.

4.1.2. Part c) recites a polypeptide comprising the extracellular domain of BCMA. Again there is no teaching in the priority document of where in the recited sequence of BCMA the extracellular domain starts and finishes.

4.1.3. There is no disclosure in the priority document of antibodies that bind to SEQ ID NO: 6 or SEQ ID NO: 8. Therefore parts g) and h) are not entitled to priority.

4.1.4. There is also no disclosure in the priority document of the fragments of SEQ ID NO: 8 as mentioned in parts m) and n) of claim 1, specifically amino acid

residues 8-37 and 1-48. Therefore parts m) and n) are not entitled to the claimed priority date.

4.1.5. By dependency on claim 1, claim 2 is not entitled to its claimed priority date.

4.2. Claim 3 is not entitled to the claimed priority date.

4.2.1. The priority document does not mention a soluble peptide comprising the extracellular domain of TACI (part b). The priority document does refer to a fragment of TACI that consists of amino acids 1-166. However, it is not clear whether this is the extracellular domain of TACI, and there is nothing which indicates whether or not this fragment is soluble.

4.2.2. Part c) recites peptide comprising the extracellular domain of BCMA. Again there is no teaching in the priority document of where in the recited sequence of BCMA the extracellular domain starts and finishes.

4.2.3. There is no disclosure in the priority document of antibodies that bind to SEQ ID NO: 6 or SEQ ID NO: 8. Therefore parts g) and h) of claim 3 are not entitled to priority.

4.2.4. There is no mention of SEQ ID Nos: 18 or 20 in the priority application. Therefore antibodies which bind to these sequences were certainly not disclosed in the priority application and so parts j) and k) of claim 3 are not entitled to priority.

4.2.5. There is also no disclosure in the priority document of the fragments of SEQ ID NO: 8 as mentioned in parts m) and n) of claim 1, specifically amino acid residues 8-37 and 1-48. Therefore parts n) and o) of claim 3 are not entitled to the claimed priority.

4.3. Claim 4 discloses fusion proteins and their use. There is no disclosure of a fusion protein comprising a peptide comprising a polypeptide having the sequence of SEQ ID NO: 8 in the priority document. The priority document does refer to a fusion protein comprising a polypeptide having the sequence of amino acids 1-150 of SEQ ID NO: 6 (which is SEQ ID NO: 8 in the Patent). However, SEQ ID NO: 8 is 184 amino acids in length and so there is no disclosure in the priority document of the fusion protein mentioned in part a) of claim 4. Furthermore, there is no disclosure in the priority document of any of the sequence fragments mentioned in parts b) to h) of claim 4. Therefore none of the features of claim 4 are entitled to priority.

4.4. None of the protein fragments mentioned in claim 5 are recited in the priority document. Therefore claim 5 is not entitled to priority.

4.5. There is no disclosure in the priority document of a soluble polypeptide comprising the extracellular domain of TACI or a polypeptide comprising the extracellular domain of BCMA. Therefore claim 6 is not entitled to priority. Fragments of TACI and BCMA comprising amino acids 1-166 and 1-150 respectively are recited, but these are not identified as extracellular domains. In any case, there is certainly no reference to the extracellular domain of TACI, or amino acid residues 1-166 of TACI being soluble.

4.6. There is no disclosure in the priority document of the fragments consisting of amino acids 1-154 of SEQ ID NO: 6 or 1-48 of SEQ ID NO: 8 as recited in claim 7. Furthermore, there is no reference to fusion proteins comprising such fragments. Therefore this claim is not entitled to priority.

4.7. Claim 8 lacks priority by dependency.

4.8. There is no disclosure in the priority document of fusion proteins comprising human Ig domains as recited in claim 9. Therefore, this claim is not entitled to priority.

4.9. Claim 10 recites the use of fusion proteins comprising a human IgG1 heavy chain constant region. No such proteins are mentioned in the priority document and so the claim lacks priority.

4.10. Claim 11 discloses the use of a medicament which comprises a multimer of fusion proteins. No medicaments comprising multimers of fusion proteins are mentioned in the priority document. Furthermore, no multimers of fusion proteins are mentioned in the priority document. Therefore, this claim is not entitled to priority.

4.11. Claims 12-14 are not entitled to the claimed priority due to their dependency on the preceding claims.

4.12. Claim 15 refers to the use of a medicament to treat resting B lymphocytes and refers back to the earlier claims. There is no reference to the use of such medicaments to treat resting B cells in the priority document. Claim 1 refers to the inhibition of ztnf4 activity. However, the description of the priority document positively teaches away from using medicaments described in the application for treating resting B cells as it states at page 51, lines 9-10, "The ligand [ztnf4] does not act on resting B cells"! Therefore claim 15 is not entitled to priority.

4.13. Claims 16 and 17 are not entitled to the claimed priority due to their dependency on the preceding claims.

4.14. Claim 18 recites multiple sclerosis as a disease that can be treated by the methods mentioned in the application. There is no mention of multiple sclerosis in the priority document and therefore this claim is not entitled to priority.

4.15. None of the disease states mentioned in claim 19 are mentioned in the priority document. The priority document does mention "renal failure", but it is not clear whether this is the same as end stage renal failure. Therefore the claim is not entitled to priority.

4.16. None of the disease states mentioned in claim 20 are present in the priority document. Therefore this claim is not entitled to priority.

4.17. Of the disease states mentioned in claim 21, only "multiple myelomas" and "lymphomas" are mentioned in the priority document. Therefore this claim lacks priority.

4.18. Claim 22 refers to the inhibition of effector T cells. The priority document refers to the use of polypeptides of the invention to modulate T cell communication. However, this is not the same as inhibiting effector T cells specifically. Therefore the claim lacks priority.

4.19. Claim 23 refers to moderation of the immune response. This particular wording does not appear in the priority document. However, the word "immunomodulation" does occur in the priority document. In any case the claim lacks priority due to its dependency on the preceding claims.

4.20. Claim 24 is not entitled to its claimed priority date due to its dependency on the preceding claims.

4.21. While immunosuppression associated with autoimmune disease is mentioned in the priority document, immunosuppression linked with other disease indications as mentioned in claim 25 cannot be found in the priority document. Therefore this claim lacks priority.

4.22. None of the disease states mentioned in claim 26 are found in the priority document and so this claim lacks priority.

4.23. There is no mention of the treatment of inflammation in the priority document and so claim 27 lacks priority.

4.24. None of the disease states mentioned in claim 28 are found in the priority document and so this claim lacks priority.

4.25. Claims 29-35 are believed to be entitled to priority.

4.26. Claim 36 refers to a number of different antibodies and fragments. However, there is no mention in the priority document of the antibodies and fragments which are specific for the polypeptides of SEQ ID NOs: 6 and 8 as mentioned in parts c) and d) of the claim. Therefore this claim is not entitled to priority.

4.27. Claims 37 and 38 lack priority by dependency.

5. Prior art in light of Priority

5.1. For those claims that are entitled to priority, D1 (von Bulow and Bram, Science, 1997, 278:138-141), D2 (Madry *et al.*, Int. Immunol, 1998, 10(11):1693-1702), D3 (WO98/27114) and D4 (WO98/39361) are full prior art. For those claims that are not entitled to priority, D5 (WO00/43032) and D6 (WO01/12812) are A.54(3) prior art.

6. Novelty

The various deficiencies in priority entitlement should be borne in mind when novelty is considered.

6.1. Claim 1 refers to the use of a number of different proteins in the manufacture of a medicament. The recitation of "for inhibiting ztnf4 activity" does not limit the claim.

6.1.1. D4 describes the TACI protein and also discloses the extracellular domain as amino acid residues 1-166 (see page 18, lines 27-28). Furthermore, this document also mentions that TACI activates signals used to initiate cell growth and division, and is involved in B and T cell development (page 56, lines 21-23). This document also describes the use of TACI in screening for ligands and making antibodies which can be used in therapy. Therefore this document describes the use of the extracellular domain of TACI (as referred to in part b) of claim 1) in the manufacture of a medicament.

6.1.2. D6 discloses the BCMA (referred to in D6 as BAFF-R) extracellular domain (page 7, lines 16-17) as referred to in part c) of claim 1. Page 15 lists a number of uses for BCMA (BAFF-R) and portions thereof, such uses including, amongst other things, the treatment of autoimmune diseases. Therefore part c) of claim 1 has been previously disclosed and therefore lacks novelty.

6.1.3. As referred to in paragraph 5.1.1, D4 describes the TACI protein and its use in therapy. From page 49, line 21 to page 52, line 16, this document also describes antibodies to TACI (i.e. antibodies that bind specifically to a polypeptide of SEQ ID NO: 6 as referred to in part g)). At page 49, lines 27-32, the document discloses that such antibodies can be used to treat diseases such as AIDS, cancers and autoimmune diseases.

6.1.4. D6 discloses BCMA (which is a receptor for BAFF, and thus is referred to in D6 as BAFF-R) and, furthermore, describes how to make antibodies that are reactive with BCMA (page 12, line 19 to page 14, line 17). This section also discloses antibody fragments as well as humanised and recombinant antibodies.

In the published claims, the use of BCMA reactive antibodies for the inhibition of B cell growth and treatment of various diseases is disclosed. Therefore part h) of claim 1 lacks novelty.

6.1.5. As mentioned in paragraph 6.1.1., D4 describes the TACI protein and also discloses the extracellular domain as amino acid residues 1-166 (see page 18, lines 27-28). Furthermore the use of this fragment as a medicament is disclosed and so part l) of claim 1 lacks novelty.

6.2. Both D4 and D6 refer to the treatment of mammals and furthermore refer to the treatment of humans (see claim 15 of D6 and page 60, line 5 of D4) which are primates. Therefore claim 2 lacks novelty.

6.3.1. As mentioned in section 6.1, the features of parts b, c, d, g, h, l and m of claim 1 lack novelty. Similarly these parts of claim 3 (note that part l) of claim 1 corresponds to part m) of claim 3) lack novelty as the claim is not in a proper second medical use format and thus is simply a use claim for the production of a medicament.

6.3.2. Part j) of claim 3 refers to an antibody that binds to BAFF (ztnf4). Such antibodies were disclosed in D5 at page 16, lines 20-21. The publication also refers to BAFF blocking agents (such as antibodies) for use in the treatment of diseases (see page 7, last paragraph). D3 also discloses the manufacture of antibodies specific for ztnf4 and their use in diagnosis and therapy (page 5, lines 1-6 and page 7, line 35 to page 8, line 1).

6.4.1. Claim 4 refer to the use of fusion proteins as medicaments. D6 discloses BCMA chimeric molecules (i.e. fusion proteins) on page 11, lines 20-25. Such molecules comprise a BCMA polypeptide or homologue thereof. The use of such BCMA polypeptides as medicaments is disclosed on page 15. Therefore part a) of claim 4 is not novel.

6.4.2. D4 discloses fusion proteins of TACI (page 7, lines 19-20) including fusions made using fragments of TACI. Such fusion proteins comprising TACI comprise the specific sequences mentioned in parts c)-e) of claim 4. D4 also describes various therapeutic uses for such TACI proteins (see page 56, line 20 to page 60, line13). Therefore parts c)-e) of claim 4 lack novelty.

6.4.3. Parts f)-h) of claim 4 refer to fusion proteins comprising fragments of BCMA. As mentioned in paragraph 6.4.1., D6 discloses BCMA chimeric molecules (i.e. fusion proteins) and such proteins comprise the BCMA fragments mentioned in f)-h) of claim 4. Therefore these parts of claim 4 lack novelty.

6.5.1. Claim 5 refers to fusion proteins of claim 4 that further comprise additional amino acid residues. Part b) recites a further sequence taken from TACI. Therefore part b) of claim 5, when taken in conjunction with parts c)-e) of claim 4 refers to a fusion protein comprising a TACI sequence. As referred to in paragraph 6.4.2. above, fusion proteins of TACI were disclosed in D4. Therefore part b) of claim 5 lacks novelty.

6.5.2. Similarly to claim 5 part b) mentioned above, part c) also lacks novelty for similar reasons over D6. This is because it refers to nothing more than a fusion protein comprising BCMA.

6.6.1. D4 describes the TACI protein and also discloses the extracellular domain as amino acid residues 1-166 (see page 18, lines 27-28). Furthermore, this document also discloses fusion proteins comprising said TACI domains (see page 7, lines 19-20). Therefore part b) of claim 6 lacks novelty as uses of such proteins in the production of medicaments are also described in D4.

6.6.2. D6 discloses the BCMA (BAFF-R) extracellular domain (page 7, lines 16-17) and fusion proteins comprising this polypeptide. Furthermore, uses of these

BAFF-R polypeptides as medicaments are also disclosed on page 15. Therefore part c) of claim 6 lacks novelty.

6.7. Claim 8 lacks novelty as D4 dislcoses a chimeric molecule comprising a TACI polypeptide and the Fc domain of an immunoglobulin (see page 24, lines 23-26). Claim 8 also lacks novelty over D6, see page 11, lines 20-25.

6.8. Claim 9 lacks novelty over D6 which discloses chimeric molecules (fusion proteins) comprising BCMA and IgG Fc domain of an immunoglobulin (page 11, lines 21-23). As it is envisaged that such fusions would be used to treat humans, the IgG domain used would be a human one.

6.9. Claim 10 lacks novelty over D6 which discloses chimeric molecules (fusion proteins) comprising BCMA and an IgG Fc domain of an immunoglobulin (page 11, lines 21-23).

6.10. Claim 13 lacks novelty over D4 which, amongst other things, describes the use of TACI, the extracellular domain of TACI and antibodies to TACI in treating B lymphocytes in order to modulate immune responses (see page 56, line 20 to page 57, line 21).

6.11. Claim 14 also lacks novelty over D4 as the B lymphocytes that are treated in this document can be activated. On page 57, lines 17-23 TACI polypeptides are described as being able to amplify B cell responses. It is only possible to amplify a response if the response is already in existence. In order for the B cells to be responding, they must be activated. Therefore D4 discloses the subject matter of claim 14.

6.12. Claim 15 lacks novelty over D4 which describes that TACI agonists (such as TACI fusion proteins) may be able to stimulate B cells. In order to be

stimulated into antibody production by the TACI polypeptide, the B cells must be resting. Therefore claim 15 lacks novelty.

6.13. D4 describes the suppression of TACI activity and therefore the suppression of unwanted immune responses by antagonising TACI (see page 58, first two paragraphs). This may be achieved using antibodies to TACI as described on page 49, lines 30-32. Therefore claim 16 lacks novelty.

6.14. Claim 17 lacks novelty over D4 for the reasons disclosed in paragraph 5.13. Autoimmune diseases are specifically mentioned in paragraph 2 of page 58 of D4.

6.15. Claim 18 also lacks novelty over D4 for the reasons disclosed in paragraphs 6.13. and 6.14. Furthermore, in paragraph 2 of page 58 of D4, the diseases systemic lupus erythematosus, myasthenia gravis and rheumatoid arthritis are specifically disclosed.

6.16. Claim 19 lacks novelty as D4 recites that TACI polypeptides may be used to treat glomerulonephritis, which is a renal disease (page 58. line 11).

6.17. Claim 20 lacks novelty over D4 as this document recites the renal disease glomerulonephritis, as mentioned in paragraph 5.16.

6.18. Claim 21 lacks novelty over D4 as this document discloses the treatment of tumors such as multiple myelomas and lymphomas (page 57, lines 24-25) with TACI agonists which are described earlier in D4.

6.19. Claim 23 lacks novelty over D4 which discloses the use of TACI polypeptides to amplify beneficial immune responses (page 57, line 17) and to treat undesirable immune responses (page 58, line 8). This is the same as

moderating immune responses as mentioned in claim 23 and thus the claim lacks novelty.

6.20. Claim 24 lacks novelty over D4. As mentioned in paragraph 6.19., this document refers to treating and downregulating unwanted immune responses. This downregulation is akin to immunosuppression as mentioned in the claim and thus the claim lacks novelty.

6.21. Claim 25 lacks novelty over D4, which describes the use of TACI polypeptides for the treatment of autoimmune and inflammatory diseases, as well as transplantation rejection and graft versus host disease (page 58, lines 8-10).

6.22. Claim 27 lacks novelty as it refers to use for the treatment of inflammation. Inflammatory diseases (therefore including inflammation) are among the conditions described in D4 that can be treated using TACI polypeptides. Therefore this claim is not novel.

6.23.1. Claim 36 lacks novelty as D4 describes pharmaceutical compositions that comprise antibodies that bind to TACI (see pages 49-52 and page 58, line 24 to page 59, line 17). Therefore the composition described in part c) of claim 36 is not novel.

6.23.2. Similarly, the composition described in part d) of claim 36 is not novel as D6 describes antibodies to BCMA (page 12, line 19 to page 14, line 17) and compositions comprising these BCMA polypeptides (page 15, line 29 to page 16, line 9).

6.24. Claim 37 also lacks novelty for the reasons given in paragraphs 6.23.1. and 6.23.2. Both of the cited passages in the cited documents explain how to produce different types of antibody including polyclonal, monoclonal and humanised antibodies.

6.25. Furthermore, claim 38 also lacks novelty as the production of antibody fragments is also disclosed in D4 and D6 as referred to in the previous three paragraphs.

7. **Inventive Step**

7.1.1. Claim 1 recites the use of a polypeptide comprising SEQ ID NO: 10. This is not inventive, as such cysteine rich sequences were identified in D2. Furthermore, figure 6 of this document shows an alignment of TACI and human and murine BCMA showing the conserved cysteine residues. Furthermore, this conserved domain was identified in D4 (see page 19, lines 20-31) and D4 also disclosed the possibility of making antibodies to TACI polypeptides (that would comprise this conserved domain) and the use of such polypeptides and antibodies in therapy. Therefore parts d) and i) of claim 1 lack inventive step.

7.1.2. Parts b) and g) of claim 1 also lack inventive step as D1 discloses TACI (both the full length and the extracellular domain) and its link with immune cells. Combining this document with common general knowledge would have lead the skilled person to create antibodies against the protein and to use the protein and such antibodies to try to modulate the immune response.

7.2. Claim 2 lacks inventive step as humans are primates and it would be an obvious aim for any researcher to try and modulate an immune response in a human once it was known that TACI is found on cells of the immune system as described in D1.

7.3. Parts b), d), g), i) and m) of claim 3 are not inventive over the prior art for the reasons given above in paragraphs 7.1.1. to 7.2. bearing in mind that the claim merely refers to the manufacture of a medicament using one of the compounds specified.

7.4. Claim 4 lacks inventive step over the prior art. As described above, it would have been obvious to use TACI polypeptides and antibodies to these polypeptides to inhibit ztnf4 activity. TACI was known in the art (see D1) and it was also known in the art that fusion proteins could be made to simplify purification and had a longer half-life *in vivo*. Therefore parts c)-e) of claim 4 lack inventive step as a fusion protein comprising TACI would comprise one of these sequences.

7.5. Claim 5 lacks inventive step as TACI was known in the art (see D1) and fusion proteins were known to improve half life and simplify purification (see D3, page 41, lines 23-24). Various fragments of TACI were also known, and it would have required nothing more than routine experimentation to see which fragments were effective in therapy.

7.6. Part b) of claim 6 lacks inventive step as the extracellular domain of TACI was known (see D1) and it was known to be linked to be a member of the TNFR family which indicates a possible use in immune modulation and therefore therapy. It was common general knowledge that fusion proteins can be made to increase half life *in vivo*. Therefore it would have been obvious to create fusion proteins comprising the extracellular domain of TACI and use them in therapy.

7.7. D4 discloses a number of different TACI fragments, and as mentioned above the use of such fragments in the manufacture of fusion proteins for use in therapy was known. D4 discloses such fusion (or chimeric) proteins at page 24, line 19 to page 25, line 28. The extracellular domain (amino acids 1-166) of TACI was known and it would have been standard practice to truncate this to see if a more effective fusion protein could be produced. Therefore claim 7 lacks inventive step.

7.8. It was well known in the art to create fusion proteins comprising the constant domain of a human IgG molecule in the production of fusion proteins (see D3, page 4, lines 24-27 and D4, page 24, line 25). Therefore claim 8 lacks inventive step.

7.9. Furthermore, it would have been obvious to use a human IgG constant domain when treating humans to reduce the risk of unwanted immunogenic reactions. D3, page 5, lines 1-3 show that such human antibodies were envisaged in this document. Therefore claim 9 lacks inventive step.

7.10. IgG1 was known in the art to be the most commonly used constant chain and was most widely tested under various conditions and so would have been the first choice of any person looking into the use of an human IgG constant domain. Therefore there is no inventive merit in claim 10.

7.11. The use of fusion proteins of TACI is not novel or inventive as indicated above. Claim 11 refers to a composition comprising a multimer of said fusion proteins. There is no definition of multimer in the Patent so it could mean that a dose of medicament contains more than one fusion protein molecule. This would be obvious to a person skilled in the art as giving one molecule of protein as a medicament would have no effect.

7.12. Claim 12 does not appear to make sense as it discloses an Ig constant region which lacks the variable region. By definition, a constant region does not have a variable region, that is why the regions are known by two different names. It therefore seems that the Patent states the obvious in this claim by claiming a constant region that has a constant domain. There is nothing in the application to define the difference between a region and a domain so this claim appears to add nothing other than to say the constant region really is constant and definitely does not have any variable regions in it!

7.13. Claim 13 is a dependent claim that defines that B lymphocytes may be treated using the methods of the invention. It would have been obvious to treat B lymphocytes, as it was suggested in D4 (page 56, lines 22-23) that the receptor was involved in their transformation.

7.14. It was known that upon activation, B cells produce various cytokines as well as antibodies. Therefore it would have been obvious to target these cells that are actively involved in signalling using TACI in the hope of modulating the response. So claim 14 lacks inventive step.

7.15. The skilled person would have realised that not only would it be beneficial to inhibit a response once it has begun, but also that it would be worthwhile to prevent a response before it has begun. Therefore it would have been obvious to treat resting B lymphocytes with TACI polypeptides to prevent any unwanted immune response from being generated in the first place. The idea of immunisation rather than prophylaxis is not new! Therefore claim 15 lacks inventive step.

7.16. As it was known that TACI was found on B cells, which produce antibodies, it would have been obvious to assume that by treating and inhibiting the action of these cells, then antibody production would be inhibited. Therefore claim 16 lacks inventive step.

7.17. D4 recites a number of conditions and disease states in which TACI could be implicated. Therefore it would be obvious to use TACI, its polypeptides, fragments and antibodies against these polypeptides for the treatment of such diseases. The diseases and conditions mentioned in D4 include autoimmune and inflammatory diseases such as glomerulonephritis, myasthenia gravis, graft rejection, rheumatoid arthritis and systemic lupus erythematosus (see page 58, lines 8-18). Furthermore, their possible use against tumors and cancers is mentioned at page 57, lines 17-27). Therefore claims 17-25 lack inventive step.

7.18. Claim 28 recites joint pain, swelling, anemia or septic shock. This is just an arbitrary selection of diseases in which inflammation is a symptom. There is no evidence to back up the claims that neutrokine-α related polypeptides can be used to treat these symptoms and therefore the claim lacks inventive step.

7.19. Claim 36 describes pharmaceutical compositions of antibodies to TACI and the consensus sequence SEQ ID NO: 10. Once these polypeptides were known, it would have required no inventive merit to create antibodies specific to them. Furthermore, once antibodies have been made, it would have been normal practice to make these into a composition that can be used in therapy. The preparation of pharmaceutical compositions is described in D1 at page 50, line 9 to page 53, line 27. Therefore claim 36 lacks inventive step.

7.20. A variety of antibody types are known in the prior art and are mentioned in claim 35. D4 also mentions in its section on antibodies (page 49, line 21 to page 52, line 16) that monoclonal antibodies and polyclonal antibodies can be made (page 50, line 3). Therefore claim 35 lacks inventive step.

7.21. Fragments of antibodies were commonly used in the art for therapy as it was known that they may clear more easily from circulation and may have better specificity than an intact antibody. This is disclosed in D4 at page 51, lines 18-23. Therefore compositions comprising such antibody fragments as mentioned in claim 38 are not inventive.

8. **Sufficiency**

8.1.1. The description in a Patent must be sufficient across the full scope of the claims. See, for example, Decisions T409/91 and T435/91. The Patent refers to the uses of a number of different polypeptides, their fragments, fusions and

antibodies. However, in most instances the claims are not supported by a clear teaching of how to use these compositions as medicaments.

8.1.2. Claim 1 lacks sufficient disclosure for a polypeptide comprising the cystein-rich pseudo-repeat (part d) and antibodies and antibody fragments that specifically bind to polypeptides comprising the motif (part i). The pseudo-repeat disclosed in the Patent, SEQ ID NO: 10, is a sequence ranging in length from 32 to 40 amino acid residues, in which only 9 amino acids are constant; the rest can vary. SEQ ID NO: 10 encompasses a large number of different sequences, for which the Patent provides no clear showing of any biological activity. The working examples in the Patent are limited to BR43x2, TACI, BCMA, and BR43x1. It is only these molecules that are shown to be capable of binding zntf4 (page 53, lines 4-10). The Patent provides no evidence that other sequences that are encompassed by the consensus sequence would bind ztnf4 and furthermore gives no way of testing if such a sequence would bind. The Patent fails to demonstrate that the motif sequence is structurally sufficient for binding to ztnf4. Therefore part d) of claim 1 is not sufficiently described.

8.1.3. Part i) of claim 1 lacks sufficient disclosure because there is no technical guidance how to make various antibodies that would (i) specifically bind to various sequences having the motif as defined in SEQ ID NO: 10 and (ii) be useful as a medicament. As stated in paragraph 8.1.2., SEQ ID NO: 10 encompasses a large number of different sequences, while the only exemplary sequences that were found to bind zntf4 are BR43x2, TACI, BCMA and BR43x1. The single working example featuring neutralizing antibodies against a protein with the motif of SEQ ID NO: 10 is Example 18, disclosing anti-TACI antibodies. This Example does not, in fact, show that the antibody produced interacts with the consensus sequence itself, but only to a protein comprising that sequence. However, part i) of claim 1 encompasses a very large number of antibodies to various molecules of unknown biological properties. Even if antibodies polypeptides other than BR43x2, TACI, BCMA, and BR43x1 were made, the

Patent fails to demonstrate that they could in fact inhibit ztnf4 activity. Further, there is no showing in the Patent that such antibodies would to treat a disease. Therefore part i) of claim 1 is not sufficiently described.

8.1.4. Claim 2 lacks sufficient disclosure for the reasons stated in paragraphs 8.1.2. and 8.1.3.

8.1.5. Claim 3 lacks sufficient disclosure because parts d) and i) are deficient for the reasons stated in paragraphs 8.1.2. and 8.1.3. There is no clear teaching in the Patent that the motif sequence, SEQ ID NO: 10, or antibodies to such a sequence would inhibit BR43x2, TACI or BCMA receptor-ztnf4 engagement.

8.1.6. Claim 4 lacks sufficient disclosure because in part a) it recites a use of a polypeptide comprising full-length BCMA (SEQ ID NO: 8). Full-length BCMA contains a cytoplasmic domain and a transmembrane domain. These domains tend to make recombinantly proteins insoluble (as has been discovered in the past). However, the Patent does not clearly teach whether or how such a protein can be produced or how they are used to prepare a medicament that works.

8.1.7. Claim 5 lacks sufficient disclosure because part c) is deficient for the reasons stated in paragraphs 8.1.6.

9. Summary

9.1. It is therefore clear that the Patent does not meet the requirements of the EPC as the claims lack novelty and inventive step with regard to the prior art and the description is insufficient.

9.2. It is therefore submitted that the request in paragraph 2.1. that the Patent be revoked is full justified.

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